

• BRIEF REPORTS •

Primary small cell carcinoma of esophagus: Report of 9 cases and review of literature

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Received: 2004-01-15 **Accepted:** 2004-02-24

Abstract

AIM: To analyze the clinical manifestations, pathological features and treatment of primary small cell carcinoma (SCC) of the esophagus and to review the literature on this entity.

METHODS: The records of 9 patients with primary esophageal small cell carcinoma were examined and the demographic data, presenting symptoms, methods of tumor diagnosis, and types of treatment given, response to treatment, pathologic findings, and clinical outcome were reviewed. Features of mixed patterns of histological differentiation and lymph node metastases were specifically sought.

RESULTS: All the patients reported dysphagia, weight loss and chest pain as the initial symptoms. In 5 cases the tumors were located in the mid-esophagus, 3 cases in the lower third of the esophagus and 1 case in the upper third. The average length of esophageal involvement was 5 cm. They underwent radical resection, regional lymph node clearance and esophageal-stomach anastomosis in thorax or at neck. Two patients had a stage IIa disease, five had a stage IIb disease, and the other two had a stage III disease of International Union Contrele Cancer (UICC). All of them were histologically and immunohistochemically confirmed SCC of esophagus. Immunohistochemical staining for neuron-specific enolase (NSE), synaptophysin (Syn) and chromogranin A exhibited strong immunoreactivity in all specimens. Three of the nine resected specimens showed foci of squamous cell carcinoma *in situ*. Metastasis was present in 7 of 9 adjacent lymph nodes. All the patients survived the operations and made an uneventful postoperative recovery. They received adjuvant systemic chemotherapy and local radiation therapy after discharge. During follow-up, three patients developed multiple liver, brain, lung and bone metastases and died between 5 and 18 mo after the diagnosis. Three patients developed widespread metastasis disease and died between 18 and 37 mo after the diagnosis. There was no local tumor recurrence in these 6 patients. The other three patients were lost during follow-up.

CONCLUSION: Primary small cell carcinoma of the esophagus is a rare but very malignant tumor. Radical resection combined with chemotherapy and radiotherapy is helpful in limited stage cases.

Wu Z, Ma JY, Yang JJ, Zhao YF, Zhang SF. Primary small cell carcinoma of esophagus: Report of 9 cases and review of literature. *World J Gastroenterol* 2004; 10(24): 3680-3682
<http://www.wjgnet.com/1007-9327/10/3680.asp>

INTRODUCTION

Primary small cell carcinoma (SCC) of the esophagus is a rare tumor characterized by early dissemination and poor prognosis if untreated^[1]. To our knowledge the standard of treatment for esophageal SCC has not been defined yet due to the paucity of cases. Treatments such as operation alone^[2], local radiotherapy^[3], chemotherapy alone^[4], or operation with adjuvant therapy^[5] have been reported. Here we described the clinical manifestations, pathological feature and treatment of 9 patients with primary esophageal SCC treated at our institution between January 1985 and December 2000 and reviewed the available literature on this entity.

MATERIALS AND METHODS

Patients with a diagnosis of SCC of the esophagus were identified from clinical and pathologic records from a 16-year period. The clinical, radiographic, and pathologic findings were reviewed and all patients in which esophageal invasion by a primary bronchial SCC could not be ruled out were excluded from the study. A total of 9 patients identified from the records were considered to have a primary esophageal SCC.

The demographic data, presenting symptoms, methods of tumor diagnosis, staging procedures done, types of treatment given, response to treatment, pathologic findings, and clinical outcome were recorded. Histological sections were reviewed to confirm the diagnosis of SCC. Features of associated carcinoma, mixed patterns of histological differentiation, and lymph node metastases were specifically sought. Immunohistochemical staining was done in differential diagnosis.

RESULTS

The study group consisted of 9 consecutive patients. There were 6 men and 3 women, with a mean age of 56 years (range from 45 to 66). All the patients reported dysphagia, weight loss and chest pain as the initial symptoms. Barium swallow, flexible esophagoscopy and biopsy established their diagnosis. Preoperative work-up excluded distant metastasis diseases in all the patients. There was no evidence of a primary bronchogenic small-cell tumor on chest radiograph. Liver ultrasonography was done before resection to exclude liver metastases. Calcium, phosphate, and alkaline phosphatase levels were measured in an attempt to exclude occult bone metastases. In 5 cases the tumors were located in the midesophagus, 3 cases in the lower third of the esophagus, and 1 case in the upper third. The average length of esophageal involvement was 5 cm (range, 3 to 7 cm).

These patients underwent radical resection, regional lymph node clearance and esophageal-stomach anastomosis in thorax or at neck. During the curative operations, all the tumors were



Figure 1 Immunohistochemical staining in SCC of esophagus (LSAB×145). A: NSE staining; B: Syn staining; C: chromogranin A staining.

confirmed to be confined to the esophagus, and the adjacent lymph nodes were either uninvolved or less than 2 cm in the greatest dimension, discrete, and within the vicinity of the primary tumor. Based on the intraoperative findings and pathological assessment, two patients had a stage IIa disease, five had a stage IIb disease, and the other two had a stage III disease of UICC. All the patients were histologically and immunohistochemically confirmed to have a SCC of esophagus. The histological criteria for small cell lung carcinoma (SCLC) proposed by the World Health Organization were used. Immunohistochemical staining for neuron-specific enolase (NSE)^[6], synaptophysin (Syn)^[7] and chromogranin A^[8] exhibited strong immunoreactivity in the specimens, which indicated that neurosecretory granules were positive in the tumor cells (Figure 1). Three of the nine resected specimens showed foci of squamous carcinoma *in situ*. All the mucosal margins were negative for tumors. Metastasis was present in 7 of 9 adjacent lymph nodes.

All the patients survived the operation and made an uneventful postoperative recovery. They received adjuvant systemic chemotherapy and local radiation therapy after discharge. The regimen of the multi-drug chemotherapy was combined with cisplatin (DDP), fluorouracil (5-Fu) and bleomycin (BLM) of 4 cycles, alternating every 3 wk. They also received radiation of the tumor bed and regional lymph nodes with the doses of 5 000 cGy at a rate of 1 000 cGy/wk. During the follow-up, three patients developed multiple liver, brain, lung and bone metastases and died between 5 and 18 mo after the diagnosis. Three patients developed widespread metastasis diseases and died between 18 and 37 mo after the diagnosis. There was no local tumor recurrence in these 6 patients. The other three patients were lost during follow-up.

DISCUSSION

Undifferentiated SCC is an aggressive tumor most frequently described in the bronchial tree, which makes up approximately 15% of all lung cancers^[9]. The most common extrapulmonary sites of SCC are the salivary glands, pharynx and larynx, esophagus, stomach, pancreas, colon, rectum, skin and cervix^[4]. To our knowledge, more than 200 cases of esophageal SCC have been described in the medical literature^[10]. The incidence of esophageal SCC ranges between 0.4–7.6% of all esophageal malignancies in different regions^[11]. In our institution, these 9 patients represented about 1% of all patients with esophageal tumors between January 1985 and December 2000.

The cellular origins of esophageal SCC have been the subject of intense speculation and debate. Esophageal SCC was initially thought to arise from argyrophilic Kulchitsky cells in esophageal mucosa^[12]. These cells have the ability to synthesize and store amines and to decarboxylate some amino acids: a feat that gave rise to the term amine precursor uptake, decarboxylation

(APUD) cells. It would now appear that esophageal SCC is of endodermal origin derived from pluripotential basal epithelial cells served as the common precursor for adenocarcinoma, squamous cell carcinoma and SCC^[13]. The small cells retain their potential for further differentiation into either mucin-producing or keratin-forming cells. This explains the coexistence of small cells, squamous and glandular elements in the same lesion. The surgical resection specimens in our group showed mixed histologic types in three out of the nine cases, all of the mixed squamous and small cell carcinomas, showed this multiple differentiation. Our findings of a high incidence of histologic heterogeneity in esophageal SCC in association with squamous carcinoma *in situ* strongly support this unified hypothesis.

Esophageal SCC may show a variety of genetic changes, including mutation of tumor-suppressor gene and loss of heterogeneity involving the genetic loci for various tumor-suppressor genes. Recent studies have shown that microsatellite instability (MSI) may be more frequent in SCC of the esophagus than in squamous-cell carcinoma of the esophagus in the development of esophageal cancer^[14]. In a previous study, we used polymerase chain reaction-polyacrylamide gel-silver stain method to investigate the presence of MSI in 3 of the 9 cases in this series and MSI was observed in 3 out of 3 cases (100%), significantly higher than squamous cell carcinoma (40.3%)^[15]. This observation suggests that the incidence of MSI and DNA replication errors may play an important role in esophageal SCC and may be an early event in esophageal SCC carcinogenesis.

Grossly, esophageal SCC was not distinguishable from esophageal squamous carcinoma. Esophageal SCC might present as an ulcerating hard tumor mass on the mucosal surface of the esophagus or as a polypoid infiltrative process growing in the submucosal layer without obvious ulceration of the mucosal surface. Microscopically, in all of the cases, the tumor was described as having a histological appearance of SCLC, consisting of round to spindle-shaped cells with scanty cytoplasm, granular nuclei, inconspicuous nucleoli, and ultrastructural and immunohistochemical evidence of neuroendocrine differentiation^[16]. The cells might be argyrophil positive with neurosecretory granules seen on electron microscopy. Immunohistologically, these cells were immunoreactive with low-molecular-weight cytokeratins and epithelial membrane antigen. Although neurosecretory granules could be identified within esophageal SCC, and they could be stained immunohistochemically for various hormones, clinical manifestations of paraneoplastic syndromes were, however, infrequent, with only scattered reports. We have not encountered paraneoplastic syndromes in the current patients.

The mean age of patients with esophageal SCC at the time of presentation, the location of esophageal SCC and presenting symptoms of esophageal SCC are similar to those of esophageal squamous cell carcinomas. But esophageal SCC is a more aggressive tumor and associated with rapid growth, and

patients usually present with widespread metastasis disease. In our series, metastasis tumor was present in 7 of 9 (78%) adjacent lymph nodes. But preoperative work-up excluded distant metastasis diseases in all the patients and all the tumors were confined to the esophagus. The resectability of these 9 cases was significantly higher than that reported by other investigators. This might be due to the advance to the advantage of early diagnosis and treatment of esophageal carcinomas.

Prospective randomized trials of therapy for esophageal SCC were unlikely given the rarity of the disease. The management of primary esophageal SCC remains controversial. Yachida *et al.*^[17], described a patient with esophageal SCC with extensive lymph node metastases. Treatment comprised a subtotal esophagectomy and extended lymph node dissection, but no chemotherapy or radiation therapy. He has survived for more than 7 years with no evidence of recurrent disease. A recent work by Casas *et al.*^[18] suggests that multimodality therapy might improve resectability and overall outcome. To allow for the evaluation of prognostic factors that influenced survival, esophageal SCC patients were grouped according to limited stage (LS), which was defined as a disease confined to the esophagus, or extensive stage (ES), which was defined as a disease that had spread beyond locoregional boundaries. There was a significant difference in survival between patients with LS and those with ES ($P < 0.0001$)^[18]. The median survival time was 8 mo for patients with LS and 3 mo for those with ES. In LS, favorable prognostic factors were the tumor size (≤ 5 cm) and the association of chemotherapy with local treatment. The best prognostic factor for ES was the feasibility of any kind of active treatment. The longest survival in our series of esophageal SCC with multimodality was 37 mo. We conclude that patients with operable diseases should be offered resection with curative intent in combination with adjuvant chemotherapy and radiation therapy.

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Edited by Zhang JZ and Wang XL Proofread by Xu FM